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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,273	03/25/2005	Gautam Vinod Daftary	24439.US	2139

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EXAMINER	
STONE, CHRISTOPHER R	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,273	DAFTARY ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER R. STONE	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,29-32,34-37,39-41,43-50 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27, 29-32, 34-37, 39-41, 43-50 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed June 16, 2008, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 27, 29, 31, 32, 34-37, 39-41, 43-50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserhati and Hollo) in view of (Links and Lewis) further in view of Zmitek et al (US Patent 5840714).

Cserhati and Hollo teaches a composition comprising cyclophosphamide (also known as cytoxan, i.e. an oxazaphosphorine of the formula of claim 27), hydroxypropyl-β-cyclodextrin (an etherified β-cyclodextrin), and water (p.70, 1st column, lines 28-34, 2nd column, lines 3-6 and p.71, Table 1, Number 16) Cyclophosphamide is taught to complex with hydroxypropyl-β-cyclodextrin (p. 72, left column, paragraph 3). Cserhati and Hollo further discloses that cyclodextrins increase the stability of guest molecules (p. 70, 1st column, line 4 and 5 and p.71, Table 1, Number 16.) Cserhati and Hollo does not disclose a pharmaceutical composition comprising the aqueous complexed hydroxypropyl-β-cyclodextrin/cyclophosphamide and mesna. Zmitek et al teaches pharmaceutical compositions comprising β-cyclodextrins complexed with an active agent, for instance piroxicam, ibuproxam and ibuprofen. In each of these cases the complex is taught to be less toxic than the active agent alone (column 2, line 66 through column 3, line 36). Links and Lewis discloses that mesna is a commonly used chemoprotective agent (i.e. protects against the known toxicities of the drugs) in patients receiving ifosfamide and cyclophosphamide (p.305, 2nd column, lines 1-3.) Therefore it would have been obvious to someone of ordinary skill in the art at the time of the instant invention, motivated by the desire to treat oxazaphosphorine-induced toxicity, to add mesna to the known aqueous hydroxypropyl-β-cyclodextrin/cyclophosphamide complex of Cserhati and Hollo since β-cyclodextrin-drug complexes were known to be less toxic than the active drug alone and mesna was a known chemoprotectant, commonly administered with cyclophosphamide, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of

success. Additionally, it would have been obvious to a person of ordinary skill in the art at the time of the instantly claimed invention to prepare the composition by mixing the components, i.e. by adding cyclophosphamide and mesna (as such or as an aqueous solution optionally containing a etherified β-cyclodextrin) to an aqueous solution of hydroxypropyl-β-cyclodextrin and optionally making up the volume with water.

The prior art renders the instantly claimed composition obvious to one of ordinary skill in the art at time of the instantly claimed invention and the optimization of composition components would have been obvious as well. Optimization of the molar substitution of Hydroxypropyl-β-cyclodextrin content and substitution would have been desired to acquire favorable complex formation. Optimization of oxazaphosphorine concentration would have been desired for optimal therapeutic effect. Optimization of the oxazaphosphorine to mesna ratio would have been desired to ensure optimal therapeutic effect with minimal urotoxicity. Applicant is reminded of in re Aller, which affirmed that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

It is obvious from the above teachings that the addition of parenteral additives to the composition at any step in the preparation would have been obvious to one of ordinary skill in the art at the time of the invention. Zmitek et al acknowledges that preparations containing β-cyclodextrins complexes can also include pharmaceutically acceptable adjuvants at their optimum concentrations (column 5, line 55 to column 6, line 34). The addition of additives such as buffers, diluents and chelators would have

been desired to adjust the pH, to maintain the pH, to adjust the volume, to adjust the concentration, and to further increase stability and is common place in the pharmaceutical art.

Filter sterilizing the composition, aseptically filling it into sterile containers and sealing the containers would have been obvious to one of ordinary skill in the art at the time of the invention. Sterility would have been desired to avoid infection caused by contaminants in the composition. Using filter sterilization would have been particularly desirable since other sterilization techniques involve heating, which may deteriorate composition components.

As noted above, Ifosfamide and cyclophosphamide were commonly used cancer drugs at the time of the invention. Therefore it would have been obvious to one of ordinary skill at the time of the invention to use the instantly claimed composition to treat a malignant disease because the therapeutically active oxazaphosphorine compounds were already commonly used for this purpose.

Claim 27 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Cserhati and Hollo), in view of (Links and Lewis), Zmitek et al (US Patent 5840714) and (Baumann and Preiss).

Cserhati and Hollo, Links and Lewis and Zmitek et al (US Patent 5840714) disclose the aforementioned inventions, but they do not disclose the composition of the instantly claimed invention comprising ifosfamide. However, the composition of the instantly claimed invention comprising the oxazaphosphorine compound cyclophosphamide is disclosed. Baumann and Preiss discloses that cyclophosphamide

and ifosfamide are the two most commonly used oxazaphosphorine compounds (p. 174, 1st column, lines 7-8.) The two compounds are isomers and share a very similar structure. Thus it would have been obvious to one of ordinary skill in the art at the time of the instant invention to use either oxazaphosphorine compound (cyclophosphamide or ifosfamide) in the composition of Cserhati and Hollo and to add mesna, since both compounds cause bladder toxicity. Thus resulting in the practice of the claimed invention with a reasonable expectation of success.

Applicant argues that Cserhati and Hollo teaches that Hydroxypropyl-β-cyclodextrin is useful to increase the hydrophilicity of hydrophobic drugs and therefore teaches away from combining Hydroxypropyl-β-cyclodextrin with ifosfamide (a hydrophilic compound). This is found unpersuasive because, as noted above, the references teaches other benefits of the complexation of Hydroxypropyl-β-cyclodextrin with compounds, including increased stability and decreased toxicity provided motivation to one of ordinary skill in the art to combine Hydroxypropyl-β-cyclodextrin with ifosfamide in a pharmaceutical composition. Additionally, as noted above, Cserhati and Hollo explicitly teaches a composition comprising complexed Hydroxypropyl-β-cyclodextrin and cyclophosphamide. Applicant is reminded of MPEP 2123 II, which states that disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). “A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.” In re Gurley, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132

(Fed. Cir. 1994) Applicant further argued that there is no motivation in Cserati or Links and Lewis to add mesna to the composition of HPBCD and cyclophosphamide. This is not found persuasive because cyclophosphamide and mesna were known in the art to be administered together, as previously made of record (Links and Lewis, p.305, 2nd column, lines 1-3.) Therefore it would have been obvious for one of ordinary skill in the art at the time of the instantly claimed invention to combine mesna and the composition of HPBCD and cyclophosphamide to administer them together. Applicant is reminded of In re Burhans, 154 F.2d 690, 69 USPQ330 (CCPA 1946) which affirmed that selection of any order of performing process steps (e.g. administering the mesna and cyclosphosphamide sequentially or combining the compounds into a composition prior to administration) is prima facie obvious in the absence of new or unexpected results. Applicant further argues that Zmitek teaches that HPBCD may decrease the toxicity of complexed compounds and that Zmitek is silent with regard to an oxazaphosphorine compound complexed with HPBCD. This is found unpersuasive because , as noted above, Cserhati and Hollo explicitly teaches a composition comprising complexed Hydroxypropyl-β-cyclodextrin and cyclophosphamide. Zmitec provides further motivation to combine the compounds into a pharmaceutical formulation by teaching that HPBCD may decrease the toxicity of complexed compounds. Applicant further argues that optimization only starts after the “process that works” is known. This is found unpersuasive because the prior art renders the instantly claimed composition obvious to one of ordinary skill in the art at time of the instantly claimed invention and the optimization of composition components would have been obvious as well for the

reasons noted above. Furthermore, Zmitek et al acknowledges that preparations containing β-cyclodextrins complexes can also include pharmaceutically acceptable adjuvants at their **optimum** concentrations and that these preparations are prepared by known methods (column 5, line 55 to column 6, line 34).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER R. STONE whose telephone number is (571)270-3494. The examiner can normally be reached on Monday-Thursday, 7:30am-4:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

11September2008
CRS

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614